Université de Montréal

A systematic analysis of the detrimental effect of hormonotherapy on skeletal and non-skeletal morbidities in male with prostate cancer

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Ce mémoire intitulé :

A systematic analysis of the detrimental effect of hormonotherapy on skeletal and non-skeletal morbidities in male with prostate cancer

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Résumé

Introduction: Plusieurs patients atteints d'un cancer de la prostate (CaP) se verront prescrire l'hormonothérapie (HT) en raison du stade avancé ou en cas d'une récidive de la maladie, pour freiner la progression de la maladie et améliorer leur survie. Cependant, l'HT présente des effets pouvant nuire significativement à la santé du patient.

Objectif : Cerner l'impact de l'HT sur l'apparition de complications squelettiques et non-squelettiques.

Méthodes : Nous avons identifié 15 842 québécois atteints du CaP. Nous avons quantifié les complications squelettiques et non-squelettiques. Les effets de l'HT ont été quantifiés à l'aide de modèles statistiques de régression tenant compte des risques compétitifs, tels que les comorbidités pré-existantes ou la mort prématurée.

Résultats : À 8 ans, l'incidence d'ostéoporose est de 4.4% chez les hommes sans HT, 10.8% chez ceux avec HT≤1.8 ans, 19.7% HT>1.8 ans et 11.4% pour les orchiectomisés. Pour la même durée, l'incidence de fracture vertébrale est de 1.9%, 7.5%, 7.5% et 8.1% pour les même groupes. Pour la fracture de hanche les taux sont de 1.9%, 6.4%, 8.0% et 9.3%, respectivement. Dans les modèles mutlivariés, l'HT >1.8 ans et l'orchiectomie augmentent significativement le risque d'évènements squelettiques. Une exposition prolongée à l'HT et l'orchiectomie augmentent le risque de détérioration cognitive. Finalement, l'HT prolongée augmente significativement le risque de maladies vasculaires périphériques et cérébrovasculaires.

Conclusions : L'hormonothérapie prolongée et l'orchiectomie augmentent significativement le risque de complications squelettiques chez les hommes québécois. Nos données confirment également l'effet de l'hormonothérapie sur le risque cardiovasculaire et sur la détérioration de la fonction cognitive.

Mots-clés : cancer, prostate, hormonothérapie, fracture osseuse, ostéoporose, démence, maladies vasculaires

Abstract

Purpose: In men with prostate cancer (PCa) androgen deprivation therapy (ADT) predisposes to skeletal-related events (SREs) defined as osteoporosis or bone fractures and non-skeletal-related (NSREs) events, such as diabetes mellitus and myocardial infarction. We tested whether this effect is also detectable within a large Canadian cohort.

Material and Methods: Within the Quebec Health Plan database we identified 15 842 men diagnosed with PCa who were treated between 1992 and 2000 with either luteinizing hormone-releasing hormone agonists [LHRHa] or orchiectomy. Separate competing-risks regression models tested the effect of orchiectomy vs. LHRHa vs. no ADT on the incident rate of three SREs and twelve NSREs.

Results: At 8 years, the incidence rates of osteoporosis were 4.4% in patients unexposed to ADT, 10.8% in LHRHa ≤1.8 years, 19.7% in LHRHa >1.8 years and 11.4% in orchiectomized patients. Similarly, the rates of spinal fracture were 1,9%, 7.5%, 7.25% and 8.1% for the same groups. Finally, the rates of hip fracture were respectively 1.9%, 6.4%, 8.0% and 9.3%. In multivariable competing-risks analyses, exposure to LHRHa >1.8 years and orchiectomy significantly increased all three SREs. Conversely, the independent predictor status was not confirmed for patients exposed to LHRHa ≤1.8 years. Moreover, prolonged LHRHa therapy increases the incidence rates of three NSREs, namely, dementia, peripheral and cerebrovascular disease (all, p≤0.02). Orchiectomy only increases the rate of dementia.

Conclusions: Exposure to prolonged LHRHa therapy or orchiectomy significantly increases the risk of SREs in Canadian men. Our results also confirm the effect of ADT on cardiovascular risks and cognitive function.

Keywords : prostate cancer, androgen deprivation therapy, skeletal fractures, metabolic complications

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Introduction

According to Statistics Canada, in 2011, prostate cancer (PCa) represented the most common cancer diagnosed in men (27.5% of new cancer cases, Fig. 1) and raked third in terms of mortality, after lung and colon cancers.[1]

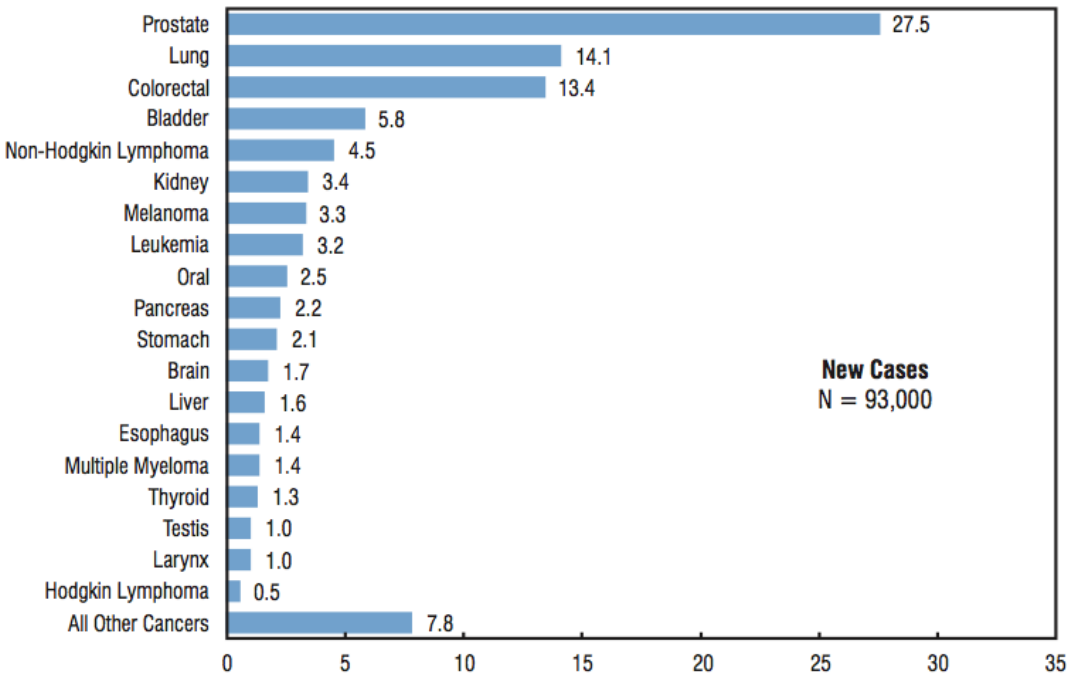

Figure 1. Percentage Distribution of Estimated New Cases and Deaths for Selected Cancers, Males, Canada, 2011.1

In Canada, 25 500 new cases were expected in 2011. In Quebec, at least 5100 new PCa cases were estimated. The natural history of PCa is more protracted that than for most other solid tumors. Its treated natural history usually spans between one or two decades, exposing cancer survivors to long period of treatments and their potential side effects.

Currently, PCa his staged both clinically and pathologically with the TNM (Tumor, Node, Metastasis) staging system (Table 1). Regular updated of this system are made to improve the classification and categorization of the patients, for clinical and research purpose. The most update system was published in 2010

by the American Joint Committee on Cancer (AJCC), in the AJCC Cancer Staging Manual, Seventh Edition, by Springer.

Table 1. TNM staging system for prostate cancer.

Primary Tumor (T)

Clinical
TX Primary tumor cannot be assessed
T0 No evidence of primary tumor
T1 Clinically inapparent tumor neither palpable nor visible by imaging
T1a Tumor incidental histologic finding in 5% or less of tissue resected
T1b Tumor incidental histologic finding in more than 5% of tissue resected
T1c Tumor identified by needle biopsy (e.g., because of elevated PSA)
T2 Tumor confined within prostate*
T2a Tumor involves one-half of one lobe or less
T2b Tumor involves more than one-half of one lobe but not both lobes
T2c Tumor involves both lobes
T3 Tumor extends through the prostate capsule**
T3a Extracapsular extension (unilateral or bilateral)
T3b Tumor invades seminal vesicle(s)
T4 Tumor is fixed or invades adjacent structures other than seminal vesicles: bladder neck, external sphincter, rectum, levator muscles, and/or pelvic wall

Regional Lymph Nodes (N)

Clinical
NX Regional lymph nodes were not assessed
N0 No regional lymph node metastasis
N1 Metastasis in regional lymph node(s)

Distant Metastasis (M)*
MX Distant metastasis cannot be assessed (not evaluated by any modality)
M0 No distant metastasis
M1 Distant metastasis
M1a Non-regional lymph node(s)
M1b Bone(s)
M1c Other site(s) with or without bone disease

In it's locally and advanced stage, the treatment of PCa requires the use of androgen deprivation therapy (ADT). The rationale of ADT in the field of PCa stems from the observations of a Canadian scientist Charles Huggins (Nobel Prize laureate 1966), who demonstrated that the male hormone testosterone is

necessary to stimulate PCa growth and its progression.[2] The latter resulted in the use of ADT, initially in the form of surgical castration (bilateral orchiectomy) and later in the form of chemical castration (luteinizing hormone-releasing hormone agonists [LHRHa]), as the mainstay therapy for locally advanced or metastatic PCa. The beneficial effects of ADT in men with locally advanced or metastatic PCa consist of delayed disease progression and palliation of disease symptoms.[3, 4] Approximately one third of all the newly diagnosed PCa cases are too advanced locally to benefit from definitive therapy or show frank evidence of metastatic disease.[5] Additionally, ADT represents a well-recognized and widely used form of therapy for localized PCa, especially in individuals with restricted life expectancy due to important comorbidities. Some 10% of newly diagnosed PCa cases fulfill the characteristics of this category of individuals.

Recently, a second formal indication for ADT was coined, when ADT efficacy was confirmed in the setting of localized PCa. Specifically, its co-administration with radiation therapy improved survival in men with unfavourable disease features.[6-9] Approximately, 25% of patients with newly diagnosed localized PCa harbour unfavourable PCa characteristics and receive ADT in adjuvant setting for between 3 and 24 months.[10] The third indication for ADT applies to patients that demonstrate disease relapse (commonly elevated and rising serum prostate-specific antigen [PSA]) after either radical prostatectomy or external beam radiotherapy for initially localized disease.[11] Five years after radical prostatectomy or radiotherapy, at least 30% of men fall into this category. Taken together, at least one in two individuals diagnosed with PCa will temporarily (in adjuvant setting) or permanently exposed to ADT. This implies that annually at least 12 750 men will receive ADT throughout Canada. Of these, more than 2500 individuals will be treated with ADT in the province of Quebec. In consequence, a large proportion of men may be exposed to ADT.

Hormonal therapy is usually administered for several years and not infrequently for decades. Therefore, the burden related to the use of ADT is not only significant epidemiologically, but has important clinical (potential side-effects) and health economics (cost of ADT: average 4500 $ / patient / syear) implications.[12] The cost of ADT may actually be higher due to its side effects. Recently, the medical literature reported an exponential rise in the type and rates of such complications. Androgen deprivation therapy for PCa in the form of orchiectomy, luteinizing hormone-releasing hormone agonists (LHRHa) and/or antiandrogens has been associated with several side effects (Fig. 2).[13] Beside the well-established side effects (loss of libido, erectile dysfunction, fatigue, hot flashes, altered body composition, etc.), recent report linked ADT to a broader range of adverse outcomes.[3, 13, 14] These consist of skeletal complications (osteopenia, osteoporosis and skeletal fractures), as well as of metabolic changes (hyperglycemia and insulin resistance, frank diabetes mellitus, hypertension, atherosclerosis, cardiovascular disease and cognitive decline).[15-22] Moreover, ADT-related side effects may undermine patient's quality-of-life and may predispose to lower life expectancy.[23-25] Even more worrisome, ADT has been associated with increased cardiovascular morbidity and mortality. To date, no study addressed the rate of skeletal and metabolic (non-skeletal) complications in a Canadian population. Currently, virtually exclusively data from the United States are used to substantiate the association between ADT and various skeletal and metabolic detriments.

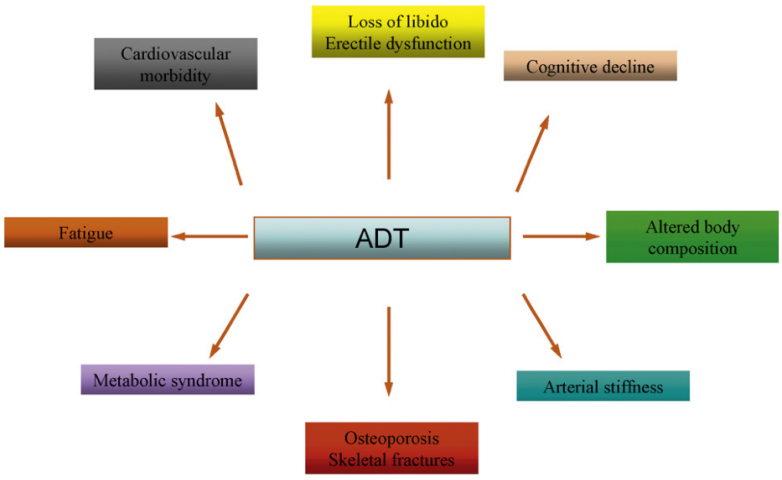

Figure 2. Side effects of androgen deprivation therapy.13

The link between ADT and fractures was addressed in one large-scale population-based analysis of the Surveillance, Epidemiology and End Results (SEER) database after linkage with Medicare records and restricted to United States male 65 years old or older (n= 50000).[15] It demonstrated a 7% absolute increase in bone fractures in PCa patients exposed to ADT. Unfortunately, no other contemporary, large-scale, population-based studies validated the effect of ADT on fracture risk or other, non-skeletal morbidities that may potentially stem from ADT. Of studies that addressed skeletal ADT morbidities, virtually all relied form the United States. Therefore, there is need for large-scale, population-based assessment of the association between ADT and fracture risk, to corroborate or refute that the suggested 7% absolute risk in skeletal complications, is of same magnitude in Canadian men.

An even grater greater paucity of data applies to several other potential ADT side effects. For example, the association between ADT and various manifestations of the metabolic syndrome were studied in only 40 patients from the United States and these data were used to propose a causal effect.[26] Based on

these sample and generalizability limitations, it is possible that other variables predispose men from the United States to many putative side effects of ADT.

Clinical observations, suggest that the rates in Quebec men might not be as elevated, as is reported in predominantly literature from the United States (for example, virtually complete absence of clinically meaningful fracture). Under this premise, several of preventive measures (bone density scans, diabetes screening, etc.) might be unnecessary. However, no reports provide factual complication rates. Based on these observations, we hypothesized that the rates of skeletal and non-skeletal side effects that are associated with ADT are not significantly higher in ADT-exposed individuals than in ADT-unexposed PCa controls. Differences in genetic, environmental, life style and dietary risk factors that distinguish Quebec men from their United States counterparts may account for these clinical observations.[27, 28] For example, fat-rich diet and higher rate of obesity, as know to affect many men from the US, may predispose to higher rates of bone loss.[29, 30] Therefore, studies from the US may exaggerate the detrimental effect of ADT on SREs. Specifically, we examined the rate of skeletal and metabolic events in patients exposed to ADT administered in the context of PCa and compared these rates to those recorded in men treated with definitive therapy (radiation or radical prostatectomy) without any ADT exposure. The practical and clinical implications of our findings may result in more specific and more selective use of ADT. This may in turn prevent side effects and save cost.

Material and Methods

The Quebec Health Plan represents the exclusive insurer in the Province of Quebec. Its database allows ascertainment of all health services covered by the Plan. These include ADT (LHRHa or bilateral orchiectomy) for patients diagnosed with PCa. The Health Plan database is used for reimbursement purposes and analyses of health services utilization. The Health Plan relies on the 9th version of the International Classification of Diseases (ICD-9) diagnostic codes and their respective dates. The Health Plan allowed us to retrieve the date of the initial diagnosis of each of the specific morbidities, namely, skeletal morbidities: osteoporosis (ICD-9 733.0), hip fracture (ICD-9 820) and spinal fracture (ICD-9 805) and non-skeletal morbidities: myocardial infarction (ICD-9 410, 411), congestive heart failure (ICD-9 398, 402, 428), peripheral vascular disease (ICD-9 440-447), dementia (ICD-9 290, 291, 294), cerebrovascular disease (ICD-9 430-433, 435), chronic pulmonary disease (ICD-9 491-493), connective tissue disease (ICD-9 710, 714, 725), ulcer disease (ICD-9 531-534), moderate to severe renal disease (ICD-9 403, 404, 580-586), diabetes (ICD-9 250), mild liver disease (ICD-9 571, 573), and moderate to severe liver disease (ICD-9 070, 570, 572).

The database provides diagnostic codes from as early on as January 1st, 1983. Follow-up information was available until July 1st, 2004. Based on stage migration, which occurred in the PSA-era, only prostate cancer cases treated after January 1st, 1992 were included. Patients diagnosed and treated after December 31st, 2000 were excluded based on length of follow-up considerations.

To assess the effect of ADT on the incidence rate of the three SREs and twelve NSREs, we queried the database for PCa patients treated with LHRHa or bilateral orchiectomy, who did not undergo any form of definitive therapy, such as radical prostatectomy (RP) or external beam radiotherapy (XRT). We also queried

for patients treated with RP and/or XRT, who were not exposed to any form of ADT. This group represented the controls.

Due to the use of reimbursement records, the database allowed exact ascertainment of LHRHa exposure, orchiectomy, RP, and definitive XRT. For orchiectomy patients, the starting point of follow-up was defined at the date of bilateral orchiectomy. For LHRHa patients, only those who filled their prescription more than 90% of the time were considered. LHRHa patients were divided according to the median duration of LHRHa exposure (LHRHa ≤1.8 years and LHRHa >1.8 years). For RP and XRT patients (controls), the starting point of follow-up was defined at RP or first XRT session.

We examined fifteen separate endpoints. Each endpoint consisted of a new diagnosis of any SREs or NSREs. Each event was assessed in separate univariable and multivariable competing-risks regression models. The analyses tested the effect of ADT exposure (LHRHa ≤1.8 years vs. LHRHa >1.8 years vs. orchiectomy vs. no ADT) on these endpoints. All analyses accounted for other-cause mortality, as described by Fine and Gray.[31] First, the incidence rates at 1, 5 and 8 years of follow-up were defined using cumulative incidence analyses that account for other-cause mortality. Subsequently, we relied on multivariable competing-risks regression models to account for the effect of other variables.

Age differences may confound more the relationship between ADT exposure and the diagnosis of SREs or NSREs. We adjusted the confounding effect of age in all multivariable competing-risks regression models. Moreover, the effect of socioeconomic status was adjusted for using the postal code and the geographic region of residence. We also adjusted for the year of treatment, since temporal trends may affect the rate of ADT associated morbidities. Finally, since other pre-

existing health conditions may predispose to additional health problems, we also adjusted for any morbidity (concomitant SRE or NSRE) that was diagnosed either before or after the beginning of follow-up. In multivariable competing-risks regression models, the dates of diagnoses of any pre-morbid conditions, if applicable, was coded as time-dependent covariates

All statistical tests were performed using S-Plus Professional, version 1.0 (MathSoft Inc., Seattle, Washington). Moreover, all tests were two-sided with a significance level set at 0.05.

Results

The descriptives of the 15842 assessable patients are shown in Table 2. The median age of the patients treated with LHRHa ≤1.8 years, LHRHa >1.8 years and orchiectomy was 7.7 to 9.4 years higher than that of their counterparts not treated with any form of ADT. The underlying comorbidities at the start of follow-up did not differ between the four groups. The effect of these and other potential differences were addressed in multivariable analyses.

Table 2. Descriptive characteristics of the study population (n=15842).

	Overall population	Patients unexposed to ADT	Patients exposed to LHRHa for ≤1.8 years	Patients exposed to LHRHa For>1.8 years	Patients treated with orchiectomy
Number of patients	15842 (100%)	10072 (63.6%)	2037 (12.9%)	1877 (11.8%)	1856 (11.7%)
Age (years)					
Mean (median)	69.1 (68.7)	66.5 (66.3)	75.2 (75.4)	75.0 (75.7)	70.2 (74.0)
Range	29.5-100.9	41.2-92.86	39.9-100.9	46.9-96.0	29.5-96.5
Charlson Comorbidity Index at the start of follow-up					
Mean (median)	2.1 (2.0)	2.0 (2.0)	2.3 (2.0)	2.1 (2.0)	2.2 (2.0)
Range	0-13	0-12	0-13	0-10	0-12
Antiandrogen therapy use	3385	0	1686 (82.8)	1699 (90.5)	0
Prevalence of morbidities					
Myocardial infarction	3628 (22.9)	2979 (20.7)	556 (27.3)	529 (28.2)	464 (25.0)
Congestive heart failure	3226 (21.6)	1725 (17.2)	601 (29.5)	574 (30.6)	526 (28.4)
Peripheral vascular disease	4074 (25.7)	2431 (24.2)	599 (29.4)	557 (29.7)	487 (26.2)
Dementia	1319 (8.4)	541 (5.4)	266 (12.0)	231 (12.3)	281 (15.2)
Cerebrovascular disease	2039 (12.9)	1176 (11.7)	303 (14.9)	309 (16.5)	251 (13.5)
Chronic pulmonary disease	4749 (29.9)	2960 (29.4)	637 (31.3)	576 (30.7)	576 (31.0)
Connective tissue disease	1048 (6.6)	659 (6.5)	131 (6.4)	152 (8.1)	106 (5.7)
Ulcer disease	2551 (16.1)	1642 (16.3)	327 (16.1)	288 (15.4)	294 (15.9)
Moderate to severe renal	1926 (12.2)	983 (9.7)	326 (16.0)	310 (16.5)	307 (16.5)
disease	4014 (25.3)	2506 (24.9)	494 (24.3)	565 (30.1)	449 (24.2)
Diabetes Mellitus	831 (5.3)	561 (5.6)	102 (5.0)	66 (3.6)	102 (5.5)
Mild liver disease	206 (1.3)	145 (1.5)	28 (1.4)	13 (0.7)	20 (1.1)
Moderate to severe liver disease					

Legend

LHRHa: Luteinizing hormone-releasing hormone agonists

ADT: androgen deprivation therapy

Figure 3 shows ADT use and type through the study period. From 1992 to 2000, almost half of patients received a form of ADT. Orchiectomy use declined significantly during this period of time, mostly due to introduction of chemical castration since 1995. For example in 1992, 39.7% were treated with orchiectomy, but in year 2000 only 6.3%.

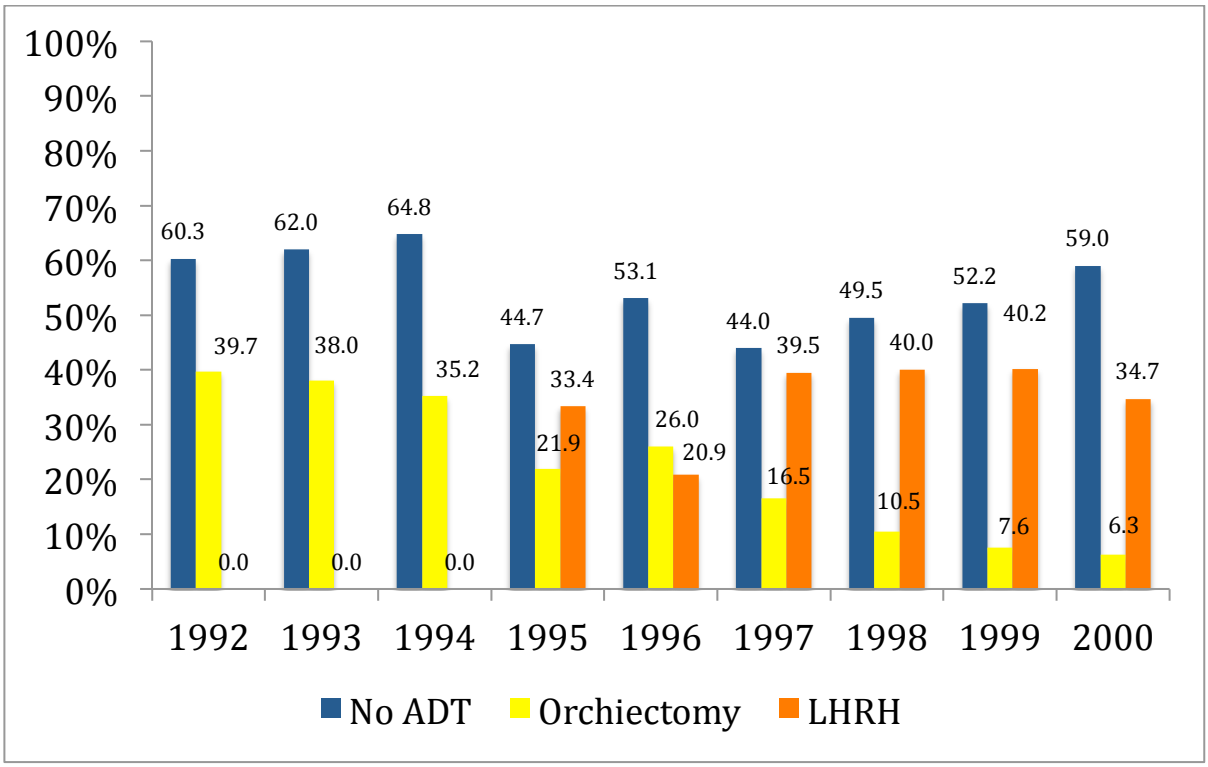

Figure 3. The type of androgen deprivation therapy used during the study period (1992-2000).

Legend

ADT: androgen deprivation therapy

LHRH: luteinizing hormone-releasing hormone agonists

Skeletal-Related Events:

Table 3 shows incidence rates of newly diagnosed osteoporosis, hip fracture and spinal fracture that were obtained from cumulative incidence models that account for the effect of other-cause mortality. For example at 8 years of follow-up, the incident rate of osteoporosis was 10.8% (95% confidence interval [CI] 8.4-13.9) in patients treated with LHRHa ≤1.8 years, 19.7% (95%CI 17.0-22.8) for those treated with LHRHa >1.8 years and 11.4% (95%CI 9.3-13.9) in patients treated with orchiectomy vs. 4.4% (95%CI 3.8-5.0) in patients unexposed to any form of ADT. For the same time-points and for the same patients groups, incident rates of spinal fracture were 7.5% (95%CI 5.6-8.2), 7.5% (4.9-8.3), 8.1% (95%CI 6.5-8.8) and 1.9% (95%CI 1.1-2.3). Similarly, the corresponding incident rates of hip fractures were 6.4% (95%CI 4.7-7.8), 8.0% (95%CI 5.3-9.9), 9.3% (95%CI 6.7-11.1) and 1.9% (95%CI 2.2-4.7) for the same four groups of patients.

Table 3. Cumulative incidence rates for skeletal-related events defined as osteoporosis, spinal fracture or hip fracture, according to type and duration of ADT (orchiectomy vs. LHRHa for ≤1.8 years vs. LHRHa for ≤1.8 years). The incidence rates account for other-cause mortality.

Osteoporosis	Duration of follow-up	1 years	5 years	8 years
No ADT	Number at risk	8205	6937	4513
	Number of events	69	135	198
	Incidence rate (%)	0.4	2.1	4.4
	95% CI	0.3-0.5	1.8-2.4	3.8-5.0
LHRHa ≤1.8 years	Number at risk	1154	775	361
	Number of events	35	67	82
	Incidence rate (%)	1.3	6.5	10.8
	95% CI	0.8-1.9	5.2-8.2	8.4-13.9
LHRHa >1.8 years	Number at risk	1733	1210	594
	Number of events	41	119	181
	Incidence rate (%)	0.9	10.1	19.7
	95% CI	0.6-1.5	8.7-11.8	17.0-22.8
Orchiectomy	Number at risk	1188	842	526
	Number of events	39	77	94
	Incidence rate (%)	1.6	7.1	11.4
	95% CI	1.1-2.4	5.7-8.7	9.3-13.9

Spinal fracture	Duration of follow-up	1 years	5 years	8 years
No ADT	Number at risk	8240	7010	4584
	Number of events	47	71	102
	Incidence rate (%)	0.3	1.1	1.9
	95% CI	0.2-0.5	0.7-1.3	1.1-2.3
LHRHa ≤1.8 years	Number at risk	1768	1284	643
	Number of events	18	45	64
	Incidence rate (%)	1.4	5.8	7.5
	95% CI	1.0-1.6	4.0-7.6	5.6-8.2
LHRHa >1.8 years	Number at risk	1154	781	369
	Number of events	44	69	74
	Incidence rate (%)	0.4	3.7	7.5
	95% CI	0.1-0.8	2.2-4.8	4.9-8.3
Orchiectomy	Number at risk	1199	865	549
	Number of events	34	59	72
	Incidence rate (%)	1.5	5.4	8.1
	95% CI	1.0-2.1	3.5-6.9	6.5-8.8

Hip fracture	Duration of follow-up	1 years	5 years	8 years
No ADT	Number at risk	8270	7031	4597
	Number of events	59	89	110
	Incidence rate (%)	0.4	1.2	1.9
	95% CI	0.2-0.8	0.8-1.5	2.2-4.7
LHRHa ≤1.8 years	Number at risk	1168	791	370
	Number of events	40	64	70
	Incidence rate (%)	1.4	5.1	6.4
	95% CI	1.0-2.0	3.8-6.2	4.7-7.8
LHRHa >1.8 years	Number at risk	1786	1294	649
	Number of events	17	47	72
	Incidence rate (%)	0.4	3.3	8.0
	95% CI	0.1-1.0	2.1-3.8	5.3-9.9
Orchiectomy	Number at risk	1198	866	545
	Number of events	45	78	88
	Incidence rate (%)	1.2	6.6	9.3
	95% CI	0.8-2.3	4.8-7.5	6.7-11.1

The results of the multivariable competing-risks regression models are shown in Table 4. In addition to adjustment for other-cause mortality, competing-risks regression models controlled for the potential confounding effect of other covariates. In models that targeted the incident rate of osteoporosis, exposure to LHRHa >1.8 years (HR: 2.3; $p<0.001$) and exposure to orchiectomy (HR: 2.3; $p<0.001$) reached independent predictor status. In models that targeted spinal fracture rate, exposure to LHRHa >1.8 years (HR: 1.9; $p=0.018$) and exposure to orchiectomy (HR: 2.2; $p<0.001$) reached independent predictor status. Finally, when hip fracture was assessed exposure to LHRHa >1.8 years (HR: 1.7; $p=0.04$) and exposure to orchiectomy (HR: 2.2; $p<0.001$) reached independent predictors status.

Table 4. Multivariable competing-risks regression models testing the effect of LHRHa or orchiectomy vs. no ADT on three separate endpoints: osteoporosis, spinal fractures and hip fractures. Each endpoint was analyzed in a separate model. Moreover, LHRHa exposure was tabulated between ≤1.8 years (median) and >1.8 years. The covariates consisted of patient age, anti-androgen exposure, postal code, region of residence, year of treatment, as well as of twelve non-skeletal morbidities that comprise the Charlson comorbidity index. Each of the Charlson comorbidities was coded as a time dependent covariate.

SREs	Osteoporosis	Spinal fracture	Hip fracture
ADT exposure	HR; p-value	HR; p-value	HR; p-value
Patients exposed to LHRHa for ≤1.8 years	1.1; 0.8	1.6; 0.06	1.3; 0.3
Patients exposed to LHRHa for>1.8 years	**2.3; <0.001***	**1.9; 0.018***	**1.7; 0.04***
Orchiectomy	**2.3; <0.001***	**2.2; <0.001***	**2.2; <0.001***

Legend

ADT: androgen deprivation therapy

SREs: skeletal-related events

LHRHa: luteinizing hormone-releasing hormone agonists

HR: Hazard ratio

*: Statistically significant

Non-Skeletal-Related Events:

Table 5 shows incidence rates of newly diagnosed twelve NSREs that were obtained from cumulative incidence models that account for the effect of other-cause mortality. For example at 8 years of follow-up, the incident rate of dementia was 8.5% (95% confidence interval [CI] 5.9-11.2) in patients treated with LHRHa ≤1.8 years, 11.3% (95%CI 8.2-14.4) for those treated with LHRHa >1.8 years and 10.2% (95%CI 8.3-12.1) in patients treated with orchiectomy vs. 3.8% (95%CI 3.2-4.3) in patients unexposed to any form of ADT. For the same time-points and for the same patients groups, incident rates of cerebrovascular disease were 4.8%

(95%CI 3.0-6.6), 7.6% (5.3-10.0), 4.4% (95%CI 3.1-5.7) and 6.2% (95%CI 5.5-6.8). Similarly, the corresponding incident rates of peripheral vascular disease were 10.5% (95%CI 6.8-14.1), 13.9% (95%CI 9.9-15.0), 8.8% (95%CI 6.9-10.7) and 8.4% (95%CI 7.6-10.3) for the same four groups of patients. For the remaining, NSREs reported on table 4, cumulative incidences throughout the study period were similar between the 4 patients groups.

Table 5. Cumulative incidence rates for twelve non-skeletal-related events according to type and duration of ADT (orchiectomy vs. LHRHa for ≤1.8 years vs. LHRHa for ≤1.8 years). The incidence rates account for other-cause mortality.

Myocardial infarction	Duration of follow-up	1 years	5 years	8 years
No ADT	Number at risk	5838	3680	1885
	Number of events	96	373	497
	Incidence rate (%)	1.5	6.0	9.2
	95% CI	1.2-1.8	5.4-6.6	8.4-10.0
LHRHa ≤1.8 years	Number at risk	386	139	21
	Number of events	16	46	48
	Incidence rate (%)	2.8	8.3	9.3
	95% CI	1.5-4.2	6.0-10.7	6.6-11.9
LHRHa >1.8 years	Number at risk	551	190	13
	Number of events	8	54	55
	Incidence rate (%)	1.4	10.3	10.7
	95% CI	0.5-2.4	7.7-13.0	8.0-13.5
Orchiectomy	Number at risk	766	417	207
	Number of events	30	71	91
	Incidence rate (%)	3.1	7.5	10.3
	95% CI	2.0-4.2	5.8-9.2	8.3-12.3

Congestive heart failure	Duration of follow-up	1 years	5 years	8 years
No ADT	Number at risk	6182	3897	2011
	Number of events	126	468	600
	Incidence rate (%)	1.8	7.1	10.3
	95% CI	1.5-2.2	6.4-7.7	9.5-11.1
LHRHa ≤1.8 years	Number at risk	396	156	21
	Number of events	27	59	62
	Incidence rate (%)	4.8	10.5	11.8
	95% CI	3.0-6.6	7.8-13.1	8.9-14.7
LHRHa >1.8 years	Number at risk	566	191	13
	Number of events	15	85	90
	Incidence rate (%)	2.3	15.3	18.3
	95% CI	1.3-3.9	12.2-18.3	14.2-22.4
Orchiectomy	Number at risk	799	443	226
	Number of events	32	90	112
	Incidence rate (%)	3.3	9.3	12.4
	95% CI	2.2-4.4	7.5-11.1	10.2-14.6

Dementia	Duration of follow-up	1 years	5 years	8 years
No ADT	Number at risk	6632	4316	2245
	Number of events	33	136	213
	Incidence rate (%)	0.5	1.9	3.8
	95% CI	0.3-0.6	1.6-2.3	3.2-4.3
LHRHa ≤1.8 years	Number at risk	460	176	28
	Number of events	17	45	49
	Incidence rate (%)	2.6	6.8	8.5
	95% CI	1.4-3.8	4.9-8.7	5.9-11.2
LHRHa >1.8 years	Number at risk	670	230	14
	Number of events	10	59	63
	Incidence rate (%)	1.5	9.5	11.3
	95% CI	0.6-2.4	7.1-11.8	8.2-14.4
Orchiectomy	Number at risk	881	474	230
	Number of events	19	79	101
	Incidence rate (%)	1.8	7.4	10.2
	95% CI	1.0-2.5	5.8-8.9	8.3-12.1

Mild liver disease	Duration of follow-up	1 years	5 years	8 years
No ADT	Number at risk	6491	4224	2221
	Number of events	26	105	132
	Incidence rate (%)	0.4	1.5	2.1
	95% CI	0.2-0.5	1.2-1.8	1.8-2.5
LHRHa ≤1.8 years	Number at risk	469	179	25
	Number of events	6	10	10
	Incidence rate (%)	0.9	1.5	1.5
	95% CI	0.2-1.6	0.6-2.5	0.6-2.5
LHRHa >1.8 years	Number at risk	674	246	14
	Number of events	1	1	1
	Incidence rate (%)	0.2	0.2	0.2
	95% CI	0.01-0.4	0.01-0.4	0.01-0.44
Orchiectomy	Number at risk	904	493	243
	Number of events	4	20	25
	Incidence rate (%)	0.4	1.8	2.4
	95% CI	0.01-0.7	1.0-2.6	1.5-3.4

Moderate to severe liver disease	Duration of follow-up	1 years	5 years	8 years
No ADT	Number at risk	6678	4364	2293
	Number of events	10	41	53
	Incidence rate (%)	0.1	0.6	0.8
	95% CI	0.05-0.2	0.4-0.7	0.6-1.1
LHRHa ≤1.8 years	Number at risk	482	188	28
	Number of events	4	4	4
	Incidence rate (%)	0.6	0.6	0.6
	95% CI	0.01-1.2	0.01-1.2	0.01-1.2
LHRHa >1.8 years	Number at risk	690	251	14
	Number of events	2	3	3
	Incidence rate (%)	0.3	0.4	0.4
	95% CI	0.01-0.7	0.01-0.9	0.01-0.9
Orchiectomy	Number at risk	928	516	251
	Number of events	1	5	7
	Incidence rate (%)	0.1	0.4	0.7
	95% CI	0.01-0.3	0.1-0.8	0.2-1.2

Moderate to severe renal disease	Duration of follow-up	1 years	5 years	8 years
No ADT	Number at risk	6449	4141	2163
	Number of events	104	302	402
	Incidence rate (%)	1.5	4.3	6.7
	95% CI	1.2-1.7	3.8-4.8	6.1-7.4
LHRHa ≤1.8 years	Number at risk	446	177	24
	Number of events	19	40	47
	Incidence rate (%)	3.0	6.5	9.7
	95% CI	1.7-4.4	4.5-8.5	6.2-13.1
LHRHa >1.8 years	Number at risk	622	223	13
	Number of events	9	57	60
	Incidence rate (%)	1.4	9.5	11.0
	95% CI	0.5-2.4	7.1-11.9	8.0-14.1
Orchiectomy	Number at risk	863	485	243
	Number of events	15	60	76
	Incidence rate (%)	1.4	5.8	7.8
	95% CI	0.7-2.1	4.4-7.2	6.1-9.6

Peripheral vascular disease	Duration of follow-up	1 years	5 years	8 years
No ADT	Number at risk	5730	3562	1831
	Number of events	122	486	618
	Incidence rate (%)	1.9	4.9	8.4
	95% CI	1.6-2.3	3.2-6.6	7.6-10.3
LHRHa ≤1.8 years	Number at risk	365	140	20
	Number of events	13	36	42
	Incidence rate (%)	2.4	7.0	10.5
	95% CI	1.1-3.8	4.9-9.2	6.8-14.1
LHRHa >1.8 years	Number at risk	537	184	12
	Number of events	12	52	57
	Incidence rate (%)	2.2	9.8	13.9
	95% CI	1.0-3.4	7.3-12.4	9.9-15.0
Orchiectomy	Number at risk	775	440	218
	Number of events	17	56	79
	Incidence rate (%)	1.8	6.0	8.8
	95% CI	0.9-2.6	4.4-7.5	6.9-10.7

Chronic pulmonary disease	Duration of follow-up	1 years	5 years	8 years
No ADT	Number at risk	5419	3418	1720
	Number of events	135	484	632
	Incidence rate (%)	2.3	8.4	12.6
	95% CI	1.9-2.6	7.7-9.1	11.6-13.5
LHRHa ≤1.8 years	Number at risk	375	138	23
	Number of events	13	35	37
	Incidence rate (%)	2.4	6.6	7.4
	95% CI	1.1-3.7	4.5-8.7	5.0-9.7
LHRHa >1.8 years	Number at risk	527	194	14
	Number of events	21	61	62
	Incidence rate (%)	3.8	10.8	11.8
	95% CI	2.2-5.4	8.2-13.4	9.0-14.6
Orchiectomy	Number at risk	771	399	204
	Number of events	21	89	107
	Incidence rate (%)	2.2	9.6	12.1
	95% CI	1.3-3.2	7.7-11.5	9.9-14.3

Connective tissue disease	Duration of follow-up	1 years	5 years	8 years
No ADT	Number at risk	6446	4172	2178
	Number of events	28	119	149
	Incidence rate (%)	0.4	1.7	2.4
	95% CI	0.3-0.5	1.4-2.0	2.0-2.8
LHRHa ≤1.8 years	Number at risk	459	179	27
	Number of events	2	8	10
	Incidence rate (%)	0.3	1.3	2.1
	95% CI	0.01-0.7	0.4-2.2	0.7-3.5
LHRHa >1.8 years	Number at risk	660	236	14
	Number of events	3	10	10
	Incidence rate (%)	0.5	1.5	1.5
	95% CI	0.01-1.0	0.6-2.4	0.6-2.4
Orchiectomy	Number at risk	897	494	240
	Number of events	2	15	18
	Incidence rate (%)	0.2	1.4	1.7
	95% CI	0.01-0.4	0.7-2.1	0.9-2.5

Ulcer disease	Duration of follow-up	1 years	5 years	8 years
No ADT	Number at risk	5867	3787	2005
	Number of events	48	187	223
	Incidence rate (%)	0.7	2.9	3.9
	95% CI	0.5-1.0	2.5-3.4	3.4-4.4
LHRHa ≤1.8 years	Number at risk	426	157	26
	Number of events	5	12	12
	Incidence rate (%)	0.8	2.1	2.1
	95% CI	0.1-1.6	0.9-3.3	0.9-3.3
LHRHa >1.8 years	Number at risk	605	221	14
	Number of events	5	19	20
	Incidence rate (%)	0.8	3.2	3.8
	95% CI	0.1-1.5	1.8-4.6	2.0-5.5
Orchiectomy	Number at risk	819	457	216
	Number of events	6	27	34
	Incidence rate (%)	0.6	2.7	3.6
	95% CI	0.1-1.1	1.7-3.7	2.4-4.7

Diabetes Mellitus	Duration of follow-up	1 years	5 years	8 years
No ADT	Number at risk	5639	3474	1786
	Number of events	97	490	632
	Incidence rate (%)	1.5	8.1	12.0
	95% CI	1.2-1.9	7.4-8.8	11.1-13.0
LHRHa ≤1.8 years	Number at risk	374	144	22
	Number of events	7	38	41
	Incidence rate (%)	1.3	7.4	8.6
	95% CI	0.3-2.2	5.1-9.7	6.0-11.2
LHRHa >1.8 years	Number at risk	548	175	5
	Number of events	14	55	59
	Incidence rate (%)	2.5	10.3	12.2
	95% CI	1.2-3.8	7.7-12.9	8.9-15.4
Orchiectomy	Number at risk	763	417	205
	Number of events	11	61	77
	Incidence rate (%)	1.2	6.6	8.9
	95% CI	0.5-1.9	5.0-8.2	7.0-10.9

Cerebrovascular disease	Duration of follow-up	1 years	5 years	8 years
No ADT	Number at risk	6301	4017	2079
	Number of events	63	285	364
	Incidence rate (%)	0.9	4.2	6.2
	95% CI	0.7-1.1	3.7-4.7	5.5-6.8
LHRHa ≤1.8 years	Number at risk	423	173	25
	Number of events	10	25	27
	Incidence rate (%)	1.6	4.1	4.8
	95% CI	0.6-2.6	2.5-5.7	3.0-6.6
LHRHa >1.8 years	Number at risk	611	213	11
	Number of events	11	39	42
	Incidence rate (%)	1.38	6.6	7.6
	95% CI	0.7-2.8	4.6-8.7	5.3-10.0
Orchiectomy	Number at risk	844	476	237
	Number of events	8	29	42
	Incidence rate (%)	0.8	2.8	4.4
	95% CI	0.2-1.3	1.8-3.8	3.1-5.7

The results of the multivariable competing-risks regression models are shown in Table 6. In models that targeted the incident rate of dementia, exposure to LHRHa >1.8 years (HR: 1.7; p=0.006) and exposure to orchiectomy (HR: 1.7; p≤0.001) reached independent predictor status. In models that targeted cerebrovascular disease rate, exposure to LHRHa for >1.8 years reached independent predictor status (HR: 1.6; p=0.02). Finally, when peripheral disease was assessed, exposure to LHRHa for >1.8 years reached independent predictors status (HR: 1.5; p=0.02).

Table 6. Multivariable competing-risks regression models testing the effect of LHRHa or orchiectomy vs. no ADT on twelve NSREs. Each endpoint was analyzed in a separate model. Moreover, LHRHa exposure was tabulated between ≤1.8 years (median) and >1.8 years. The covariates consisted of patient age, anti-androgen exposure, postal code, region of residence, year of treatment and other comorbidities. Each comorbidity was coded as a time dependent covariate.

NSREs	Myocardial infarction	Congestive heart failure	Dementia	Cerebro-vascular disease	Chronic pulmonary disease	Ulcer disease	Diabetes mellitus	Mild Liver disease	Peripheral vascular disease	Moderate to severe Liver disease	Connective tissue disease	Moderate to severe renal disease
ADT exposure	HR; p-value	HR; p-value	HR; p-value	HR; p-value	HR; p-value	HR; p-value	HR; p-value	HR; p-value	HR; p-value	HR; p-value	HR; p-value	HR; p-value
LHRHa for ≤1.8 years	1.1; 0.7	1.1; 0.9	1.4; 0.06	1.5; 0.05	0.9; 0.3	1.1; 0.5	0.8; 0.5	0.9; 0.1	1.4; 0.07	1.0; 0.3	0.9; 0.2	1.2; 0.3
LHRHa for r>1.8 years	1.2; 0.5	1.5; 0.06	**1.7; 0.006***	**1.6; 0.02***	1.1; 0.1	1.1; 0.6	1.1; 0.3	0.75; 0.08	**1.5; 0.02***	0.9; 0.6	0.8; 0.5	1.4; 0.06
Orchiectomy	1.1; 0.2	1.1; 0.3	**1.7;<0.001***	0.9; 0.3	1.03; 0.8	0.8; 0.3	0.9; 0.3	1.02; 0.9	0.9; 0.2	0.9; 0.9	0.8; 0.3	1.06; 0.6

Legend

ADT: androgen deprivation therapy

NSREs: non-skeletal-related events

LHRHa: luteinizing hormone-releasing hormone agonists

HR: Hazard ratio

*: Statistically significant

Discussion

Prostate cancer (PCa) is the most commonly male malignancy and is the second leading cause of cancer related death in North American men. However, rates of non-cancer deaths in men with prostate cancer are greater than in the general population and ADT treatment may, in part, be responsible for this increase.[32] Moreover, a recent communication found that long-term LHRHa exposure was associated with greater non-cancer mortality than short-term LHRHa therapy.[33] Furthermore, Keating et al. recently demonstrated that ADT increases the risk of incident diabetes, coronary heart disease, acute myocardial infarction, and sudden cardiac death.[18] Moreover, several studies have demonstrated the deleterious effect of hormonal suppression on bone-health.[34, 35 36 37] Virtually all large studies that addressed this topic were performed in the United States of America, where genetic, environmental and dietary risk factors may substantially differ from other part of the world. For example, obesity and PCa may exert a synergic effect on the rate of SREs.[38, 39] Since obesity rate is higher in the US than in Europe or Canada, SREs may be more frequent in the US.[40] Finally, recent studies highlighted the increasing trend in ADT prescriptions for localized PCa, even in absence of any evidence-based benefit.[41] Based on these observations, we tested the hypothesis that ADT may increase the risk of developing new non-cancer morbidities in a large population based cohort of patients treated for PCa with or without ADT. We tested this hypothesis by quantifying the rate of these established SREs and NSREs in Canadian men.

Our results indicated that LHRHa exposure in excess of the median duration (1.8 years) significantly predisposes to higher rates of SREs. At 8 years of follow-up, men exposed to LHRHa duration >1.8 years demonstrated a near 4-fold higher rate of SREs relative to men unexposed to ADT. Similarly, we found a near 2-fold increase in SREs rates in men exposed to orchiectomy. Interestingly, highest incident rates of SREs were recorded men treated with orchiectomy and those

exposed to LHRHa >1.8 years. Conversely, the SREs recorded in patients exposed with LHRHa ≤ 1.8 years (median) failed to demonstrate statistically significant differences from those recorded in patients unexposed to ADT. Taken together, our findings imply that LHRHa duration >1.8 years and orchiectomy treatment had the most detrimental effects on SREs rates.

In the analyses of spinal and hip fracture rates, orchiectomy was either more or equally detrimental to LHRHa exposure duration >1.8 years. Conversely, ADT exposure of ≤1.8 years duration was invariably less detrimental than >1.8 years of exposure or orchiectomy treatment. This observation is important from a clinical perspective as it suggests that intermittent ADT might be less deleterious than continuous ADT. Although this hypothesis is attractive it remains to be proven in randomized clinical trials.

Our results also show that for most of the NSREs, no significant differences in incidences rates were recorded after 8 years of follow up between men exposed compared to those unexposed to any type of ADT. This questions the detrimental effect of ADT on several metabolic morbidities, such as cardiovascular disease and diabetes mellitus. However, our data showed that patients exposed to LHRH for more than 1.8 years had near 2-fold higher risk of for peripheral and cerebrovascular disease then those unexposed. Multivariable models targeting the effect of ADT on vascular disease also confirm the detrimental effect of ADT on the vascular health of men exposed to ADT. Moreover, our results also confirmed the effect of ADT on cognitive decline, where men exposed to both prolong LHRH exposure and orchiectomy had more than 2-fold higher rates of dementia then men unexposed.

The novelty of our findings is several-fold. Our analysis is the first to control for other-cause mortality. Lack of accounting for mortality due to PCa or other-

causes may artificially overestimate the effect of ADT on SREs. Cumulative incidence and competing-risks regression analyses control for the confounding effect of mortality. This is particularly important in elderly patients, as patients who die prematurely have no chance of experiencing the adverse outcome of interest i.e., one or several SREs.

Elderly patients may also be affected by comorbidities. These may in turn lead to discontinuation of LHRHa. Such practice may also confound the true effect of ADT on SREs, as patients with multiple comorbidities may not be given an equal chance of being exposed to ADT and an equal chance of being diagnosed with one or several SREs. Our analysis controlled for comorbidities.

Additionally, our analyses also controlled for other known confounders, such as age, anti-androgen exposure, postal code, region of residence, and year of treatment. Interestingly, although we considered exposure to anti-androgen, this variable failed to affect the rates of SREs. It could have been postulated that anti-androgens might protect from SREs.

Our study is not devoid of limitations. First, its design is not prospective. Therefore, the ascertainment of diagnoses may be subject to underreporting. Not all conditions might have been identified using diagnostic codes. However, it is unlikely that there are differences in the rate of reporting of diagnostic codes according to orchiectomy exposure status. Therefore, it is also unlikely that the relative measures of risk have been affected by differential misclassification bias. Similarly, the ascertainment of exposure (LHRHa vs. orchiectomy vs. no ADT) is unlikely biased, as LHRHa medication codes and orchiectomy reimbursement codes were used for exposure definition. It is unlikely that reimbursement would not be sought in orchiectomized patients or that dispensed LHRHa injections would not be used.

Universal access to health care represents a weakness, as well as an advantage of the current design. Access to orchiectomy in the Province of Quebec is not dictated by health insurance status. Nonetheless, the socioeconomic status (education) and temporal trends may have affected the rate of orchiectomy use [42]. In consequence, we adjusted for both variables. The adjustment for year of treatment likely decreased or eliminated the confounding effect of temporal trends. However, adjustment for socioeconomic status by proxy of region of residence and postal code may not have completely eliminated the effect of socioeconomic status. Moreover, our analyses were limited by lack of consideration of several pharmacological agents aimed at SRE prevention, such as calcium, vitamin D or bisphosphonates.

Finally, the administrative nature of our database precluded the consideration of disease stage. In consequence, it cannot be entirely excluded that orchiectomy patients by virtue of more advanced disease stage are not predisposed to higher rates of myocardial infarction and/or dementia. However, there is no evidence for such association and there is no biologic rationale for its existence.

Despite these limitations, our findings provide valuable information about potential detriments of ADT exposure. They should be used in treatment decision-making when ADT exposure is considered.

Conclusion

In conclusion, exposure to prolonged LHRHa therapy significantly increases the incidence rates of osteoporosis, spinal and hip fractures in Canadian men. Moreover, of twelve morbidities, exposure to prolonged LHRHa therapy increases the incidence rates of only three of them, namely: dementia, peripheral vascular disease and cerebrovascular disease. These findings confirm the detrimental effect of LHRHa on fracture rates in men from outside of the US. These results also confirm the effect of ADT on cardiovascular risks and cognitive function. Although the effect is weak, it still warrants caution in the setting of pre-existing morbidities when ADT is considered. Orchiectomy is associated with higher incidence rates of osteoporosis, spinal and hip fractures. Preventive or therapeutic measures should be considered if this treatment modality is chosen. However, of twelve morbidities, orchiectomy was associated only with higher incidence rates of dementia.

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